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Conserved outer membrane protein of *Neisseria meningitidis* involved in capsule expression

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In *Neisseria meningitidis*, translocation of capsular polysaccharides to the cell surface is mediated by a transport system that fits the characteristics of ABC (ATP-binding cassette) transporters. One **protein** of this transport system, termed CtrA, is located in the **outer membrane**. By use of a CtrA-specific monoclonal antibody, we could demonstrate that CtrA occurs exclusively in *N. meningitidis* and not in other pathogenic or nonpathogenic *Neisseria* species. Nucleotide sequence comparison of the ctrA gene from different meningococcal serogroups indicated that CtrA is strongly conserved in all meningococcal serogroups, independent of the chemical composition of the capsular polysaccharide. Secondary structure analysis revealed that CtrA is anchored in the **outer membrane** by eight **membrane-spanning** amphipathic beta strands, a structure of **proteins** that function as porins.

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Emerging Strategies in the Fight Against Meningitis: Molecular and Cellular Aspects

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Nisseria meningitidis colonises approx 10% of the population without causing disease. However it can also invade the host resulting in one of the most aggressive bacterial infectious diseases known to occur in humans. Invasive meningococcal disease is characterised by high fatalities i.e. between 5% and 10% and may exceed 50% in the absence of prompt diagnosis. In this book Internationally renown authors review the current understanding of factors involved in meningococcal infections and the current strategies being used to fight infection. Topics covered include the interaction of the bacterium with host cells and the immune system, meningococcal population studies, and strategies for the development of an effective vaccine.

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Chapter 1: The Role of the Leptomeninges in Meningococcal Meningitis

Myron Christodoulides, John E. Heckels and Roy O. Weller

Abstract

The molecular basis of the interactions between *Neisseria meningitidis* and cells of the central nervous system is poorly understood. Meningococci show a specific predilection for binding to the human leptomeninges (arachnoid mater, arachnoid trabeculae and pia mater) in the subarachnoid space (SAS). Leptomenigitis induced by meningococci is characterised by an acute, compartmentalised inflammatory response confined largely to the SAS, with little or no involvement of the underlying brain. Recently, the role of the leptomeninges in meningococcal leptomenigitis has been the subject of intense investigation. This has been possible only with the development of an in vitro meningioma cell culture model that mimics the leptomeninges *in vivo*. In this article, we describe the nature of the surface ligands present on meningococci that mediate interactions with meningioma cells, and demonstrate that meningeal cells are not passive, but active participants in the inflammatory response and host cellular defence. However, despite this increase in knowledge regarding the pathophysiology of meningococcal leptomenigitis, many questions still remain unanswered. This article concludes by addressing these questions, which form the basis of future investigations in this neglected field.

Chapter 2: Informative Talk Between *Neisseria meningitidis* and Host Cells

Muhamed-Kheir Taha and Ala-Eddine Deghmane

Abstract

Adhesion of *Neisseria meningitidis* to target cells provokes a complex bacterium-cell cross talk. *N. meningitidis*-cell interaction begins with initial (localised) adhesion then it progresses toward intimate adhesion that involves close contact between *N. meningitidis* and the target cell membrane. During this interaction, modifications in both bacteria and target cells are observed. Contact between *N. meningitidis* and viable cells seems to be a signal that promotes the effective adhesion process. As in target cells, signal transduction pathway in bacteria may involve a network of regulators acting in cascade. The expression of bacterial surface structures interfering in adhesion such as pili and capsule seems to be modulated. CrgA, a

new bacterial LysR-like transcriptional regulator that could be a member of this network. CrgA seems to be involved in a co-ordinate regulation of bacterial genes to permit the switch between initial and intimate adhesion. The activation of both bacteria and target cells through signal transduction pathways is therefore a key element in neisserial pathogenesis.

Chapter 3: Interactions with the Immune System

Oliver Billker, Sigrid Gödert, and Thomas F. Meyer

Abstract

Like with any highly adapted pathogen, interactions between *N. meningitidis* and the human immune system have many different facets. An encounter with meningococci may be characterised by complete immunity but often results in transient, asymptomatic colonisation of the nasopharyngeal mucosa. However, it can also lead to systemic meningococcal disease. In each case different types of interactions between meningococci and the human immune system prevail. Meningococcal virulence factors such as the polysaccharide capsule, lipooligosaccharides, type IV pili, porins, adhesins and IgA1 protease, may have important functions for colonisation and penetration of the mucosal barrier and for the evasion of human immune mechanisms. Many of these and other meningococcal proteins and surface structures display a remarkable degree of antigenic and functional variation. This variation is generated at the gene level by diverse molecular mechanisms that rely on strand slippage during replication, natural competence for transformation, intragenomic gene conversion, and a transposable genetic element. Meningococci-specific bactericidal antibodies, which are induced by meningococcal carriage or vaccination, are essential for a protective humoral immune response that restricts colonisation to the mucosal surface and prevents systemic disease. During invasive disease meningococcal endotoxin and probably other factors induce high levels of TNF α and other proinflammatory cytokines that are key mediators of meningococcal pathogenesis.

Chapter 4: *Neisseria meningitidis*: Multiple Mechanisms to Acquire Iron

Andrew R. Gorringer and Jonathan Oakhill

Abstract

Iron is a nutrient of vital importance to the meningococcus, which is clearly evidenced by the multiple receptor proteins and uptake systems possessed by the organism. These mechanisms will come into play when the meningococcus is present in various host environments, including mucosal surfaces, blood and cerebro-spinal fluid. The meningococcus possesses surface receptors for the human iron proteins transferrin (TbpA+B), lactoferrin (LbpA+B) and haemoglobin (HmbR, HpuA+B) and a receptor for the exogenous siderophore enterobactin (FetA). TbpA, LbpA, HmbR, HpuB and FetA share homology with TonB-dependent outer membrane porins such as the *Escherichia coli* siderophore receptors FepA and FhuA, whose structures have been solved. TbpB, LbpB and HpuA are thought to be peripherally-associated with the outer membrane and facilitate the initial binding of the iron protein. TbpA, LbpA and FetA are thought to allow the passage of iron to the periplasm where it is transported to the cytoplasm via the FbpABC transporter. The haemoglobin receptors allow passage of haem to the periplasm where it is transported across the inner membrane utilising a permease and ATPase. Expression of most of these iron uptake

proteins is regulated by the repressor protein Fur, which uses iron as co-repressor. The expression of these multiple iron uptake systems reflects the complex interaction of the meningococcus with its host as commensal and pathogen, capable of causing septicaemia and/or meningitis.

Chapter 5: Outer Membrane Vesicles and Other Options for a Meningococcal B Vaccine

J.T. Poolman, C. Feron, G. Dequesne, P.A. Denoël, S. Dessoy, K.K. Goraj, D.E. Janssens, S. Kummert, Y. Lobet, E. Mertens, D.Y. Monnom, P. Momin, N. Pépin, J.-L. Ruelle, J.J. Thonnard, V.G. Verlant, P. Voet, and F.X. Berthet

Abstract

The development of a menB vaccine is difficult. Outer membrane vesicles derived from wild-type strains were found to be protective in teenagers in homologous settings. From Brazilian studies evidence has been obtained that protection > 4 years can be observed with a monovalent wild-type OMV vaccine even in epidemiological situations characterized by multi-strain endemic disease. With such OMV vaccines, the serum bactericidal activity (SBA) results demonstrate serosubtype (PorA) specificity, particularly in infants. Ongoing research has identified potential cross-bactericidal activity inducing menB antigens. This research has recently been supplemented by the possibility to identify antigens from available full genomic sequences. The challenge is to find the right combination of antigens in order to develop a generic crossreactive menB vaccine.

Chapter 6: Population Structure of *Neisseria meningitidis*

M.C.J. Maiden

Abstract

A number of features of the natural history and population genetics of *Neisseria meningitidis*, which is responsible for both meningitis and septicaemia world wide, impact on the epidemiology of meningococcal disease. Paradoxically for an organism well known as an aggressive pathogen, the majority of infections by this bacterium result in harmless colonisation rather than invasive disease. A further level of complexity is added by the fact that meningococcal populations are highly diverse and only a minority of the genotypes present in carrier populations are regularly associated with disease. These 'hyperinvasive lineages' include the subgroups of serogroup A meningococci, which are responsible for epidemic and pandemic disease in Africa and Asia, while other genetic lineages cause sporadic outbreaks of disease world wide (the ET-37 complex and the A4 cluster) or hyperendemic disease (ET-5 complex and lineage 3). In the Americas and Europe, high carriage rates of meningococci are accompanied by cycles of infection caused by different lineages, which presumably correspond to the cyclic spread of the hyperinvasive lineages in carriage. The introduction of high-throughput nucleotide sequence determination for the identification of lineages, large-scale carriage studies and the application of phylogenetic and theoretical techniques, provide the data and methods necessary for an improved understanding of meningococcal population structure. This information can be used to develop and assess the likely impact of public health interventions such as vaccination.

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